Recruitment of Lung Diffusing Capacity*
Update of Concept and Application

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Lung diffusing capacity (DL) for carbon monoxide (DLCO), nitric oxide (DLNO) or oxygen (DLO2) increases from rest to peak exercise without reaching an upper limit; this recruitment results from interactions among alveolar volume (VA), and cardiac output (Q), as well as changing physical properties and spatial distribution of capillary erythrocytes, and is critical for maintaining a normal arterial oxygen saturation. DLCO and DLNO can be used to interpret the effectiveness of diffusive oxygen transport and track structural alterations of the alveolar-capillary barrier, providing sensitive noninvasive indicators of microvascular integrity in health and disease. Clinical interpretation of DL should take into account Q in addition to VA and hemoglobin concentration.

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Key words: cardiac output; diffusion-perfusion ratio; erythrocyte; exercise; hypoxemia

Abbreviations: CHF = congestive heart failure; DL = lung diffusing capacity; DLCO = lung diffusing capacity for carbon monoxide; DLNO = lung diffusing capacity for nitric oxide; DLO2 = lung diffusing capacity for oxygen; DM = membrane diffusing capacity; DMCO = membrane diffusing capacity for carbon monoxide; NO = nitric oxide; Q = cardiac output; SaO2 = arterial oxygen saturation; ScO2 = end-capillary oxygen saturation; VA = alveolar lung volume; Ve = pulmonary capillary blood volume; 1/ΘNO = erythrocyte resistance to nitric oxide uptake; Δt = transit time of blood through the lung; Θ = rate of gas uptake by whole blood

Lung diffusing capacity (DL) is known to vary with hemoglobin concentration and alveolar lung volume (VA). Standard equations are routinely applied to empirically correct measured DL to a constant hemoglobin concentration, and the DL/volume ratio (transfer factor) is commonly used to distinguish whether a low DL reflects parenchymal disease or volume restriction.1 In contrast, DL can more than double as cardiac output (Q) increases from rest to peak exercise in normal subjects; the increase results from recruitment of unperfused or unevenly perfused capillary reserves as Q rises, and unfolding of alveolar septa as lung volume increases. Recruitment is critical for maintaining a normal arterial oxygen saturation (SaO2) as oxygen uptake increases. The effectiveness of recruitment can be described by how the DL/Q ratio changes as exercise load increases; when the DL/Q ratio declines below a critical level, SaO2 falls. Recent advances examining the determinants of the DL/Q ratio within the alveolar-capillary bed in health and disease and from rest to exercise have not only modified the conventional interpretation of DL but also consolidated the physiologic basis for its clinical application. This article updates the current concepts and practical relevance of the DL/Q interaction, with the goal of facilitating the judicial use and interpretation of DL as well as its components, membrane diffusing capacity (DM) and capillary blood volume (Ve).

Physiologic and Structural Basis of DL Measurement

DL is the conductance of oxygen (DL for oxygen [DLO2]) or carbon monoxide (DL for carbon monoxide [DLCO]) from alveolar air to capillary hemoglobin. The reciprocal (1/DL) is the resistance to gas transfer across the barrier. Roughton and Forster2 conceptualized two independent resistances arranged in series, i.e., overall resistance (1/DL) is the sum of resistances imposed by the alveolar-capillary membrane (1/DM) and blood [(1/Θ) X Ve], as shown in equation 1,

\[
\frac{1}{DL} = \frac{1}{DM} + \frac{1}{\Theta \times Ve}
\]

where Θ is the rate of gas uptake per Torr of pressure gradient per milliliter of whole blood mea-
sured in vitro. For carbon monoxide, resistances of the membrane and erythrocyte contribute almost equally to overall diffusive resistance. Since oxygen and carbon monoxide compete for the same heme binding sites, Θco is inversely related to alveolar oxygen tension and directly related to hemoglobin concentration. DM for carbon monoxide (DMCO) and Vc can be estimated from DLco measured at two or more inspired oxygen tensions. Equation 1 implicitly assumes the following: (1) diffusive resistance in the alveolar gas phase is negligible, (2) there is no interaction between septal tissue and erythrocyte membranes, and (3) alveolar oxygen tension does not significantly affect DMco or Vc.3

The alveolar septum consists of about 55% tissue and 45% capillary blood,4 with erythrocytes acting as discrete sinks for gas uptake. DM is related directly to the available alveolar-capillary surface area and inversely to the mean harmonic thickness of the tissue-plasma barrier, as shown in equation 2:

\[ DM = k \times \frac{\text{surface area}}{\text{barrier thickness}} \]

where \( k \) is the diffusion constant, a function of gas permeability in lung tissue and plasma. The rate of diffusion is the product of DL and the gas partial pressure gradient across the barrier. Anatomically, surface area, barrier thickness, and Vc can be estimated using morphometric techniques in fixed lungs.3 DL estimated from morphometric measurements of DM and Vc agree well with that measured physiologically at peak exercise.6 This close structure-function correlation reflects large physiologic reserves of DL that are not utilized at rest. The capacity for diffusive transport, determined by lung structure, is not approached normally except at peak exercise; this observation has important implications with regard to interpreting resting DL measurements, as explained later.

Small amounts of inhaled nitric oxide (NO)7,8 have also been used to measure diffusing capacity for NO (DLNO). The ferrous binding sites of hemoglobin scavenge NO with an affinity of approximately 8,000 times a reaction velocity about 250 times that for carbon monoxide; at the same time, the diffusion coefficient in water for NO and carbon monoxide are similar, and the solubility of NO in water is only twice that for carbon monoxide. Hence, relative to DLco, DLNO reflects predominantly diffusive resistance of the tissue-plasma barrier; the contribution of erythrocyte resistance to NO uptake (1/ΘNO) is small enough that for practical purposes it can be neglected, i.e., 1/ΘNO ≈ 0, and DLNO = DM for NO (DMNO). The expected DLNO/DMCO ratio is 1.93 based on the solubility and molecular weight of NO and carbon monoxide.9 We found a strong linear correlation between DLNO and DMCO \( (r^2 = 0.87) \), with a mean DLNO/DMCO ratio of 2.49 in normal subjects at rest and during exercise.10 The 29% higher-than-expected ratio is in the wrong direction to be explained by an underestimation of 1/ΘNO; it could reflect known variability in the assumed Θ for carbon monoxide (ΘCO) used to calculate DMCO11 or in assumed gas solubility in plasma. Combined measurement of DLNO and DLco could potentially allow simultaneous estimation of DM and Vc during exercise in a single maneuver. If DMCO and Vc are known, DLO2 can be estimated by equation 3:

\[ \frac{1}{DLO_2} = \frac{1}{1.23 \times DMCO} + \frac{1}{3.9 \times Vc} \]

where the relative diffusivities of oxygen to carbon monoxide in solution are 1.23, and Θ for oxygen \( (ΘO_2) \) measured in whole blood is 3.9 mL/(minute·Torr·milliliter of blood) \(-1,12 \) DLO2 can also be measured independently from arterial oxygen exchange using the multiple inert gas elimination technique13; the resulting relationship between DLO2 and \( \dot{Q} \) is similar to that derived from equation 3,11 indicating that DLO2 estimated by different methods are internally consistent. Hence, the relationships of DLO2 and DLNO to \( \dot{Q} \) can be used to evaluate the functional significance of diffusive oxygen transport from rest to exercise.

**Recruitment of DL and Its Determinants**

From rest to peak exercise, DLco, DLNO, DLO2, DMCO, and Vc all increase linearly with respect to \( \dot{Q} \) without reaching an upper limit (Fig 1).10,11,13,14 Recruitment of DL arises from several sources: (1) unfolding and distension of alveolar septa as the...
lungs expands, (2) opening and/or distension of capillaries as \( Q \) increases, (3) increased capillary hematocrit, and (4) more homogeneous distribution of erythrocytes within and among capillaries. \( DL \) also increases by up to 25\% with increasing \( V_A \), and exhibits hysteresis similar to that in the transpulmonary pressure-lung volume relationship. The number of perfused alveolar capillaries increases directly with perfusion pressure, which increases \( V_c \) and capillary surface for gas uptake. \( V_c \) increases as central blood volume increases during exercise, saline solution infusion or microgravity. Less recognized are interactions between changing shape, distribution, and spacing of capillary erythrocytes on \( DL \) recruitment, as discussed below.

Erythrocyte Spacing (Hematocrit)

Dinakara et al. observed a direct relationship between resting \( DLCO \) and hemoglobin concentration, and derived an empirical correction factor; Marrades et al. offered another linear correction. Cotes et al. derived a nonlinear equation to adjust \( DLCO \) to a standard hemoglobin concentration using equation 1, assuming \( \Theta CO \) is proportional to hemoglobin concentration and \( DMCO/V_c \) is constant, i.e., erythrocyte volume affects only erythrocyte resistance \([1/(\Theta CO \times V_c)]\) but not membrane resistance \((1/DMCO)\). However, recent evidence shows that membrane and erythrocyte resistances are interrelated quantities and hematocrit affects both. Highly aerobic animals (e.g., dogs) show significantly higher intercept as well as steeper slope in the \( DLCO \) and \( DMCO \) vs \( Q \) relationships than humans; the higher intercept is due to larger lung volume and alveolar-capillary surface areas per unit of body mass, while the higher slope is attributable to splenic contraction in aerobic animals that increases systemic hematocrit from rest to peak exercise by up to 30\% above baseline values. Mathematical simulations of carbon monoxide diffusion show a nonlinear relationship between capillary hematocrit and \( DMCO \) when other variables are held constant. At a low hematocrit, only a small fraction of alveolar-capillary membrane in close proximity to the erythrocyte membrane participates in carbon monoxide uptake (Fig 2). As hematocrit increases, more available alveolar-

**Figure 2.** Tissue-erythrocyte interaction illustrated by simulated carbon monoxide uptake across a geometric model of pulmonary capillary using finite element analysis and principles of heat exchange. Erythrocytes are considered infinite sinks for carbon monoxide. Direction and size of arrows indicate the direction and magnitude of carbon monoxide flux. At a low hematocrit, only a small fraction of available alveolar-capillary surface participates in carbon monoxide uptake. As erythrocyte density (hematocrit) increases, more available surface becomes utilized and effective membrane conductance \((DM)\) increases. From Hsia et al.
capillary membrane participates in carbon monoxide uptake, thereby increasing effective DMCO. This tissue-erythrocytes interdependence creates potential errors in the relationship described by Roughton and Forster.2 Dynamics of erythrocyte flow is difficult to study in humans; animal studies have demonstrated large regional variations in pulmonary capillary hematocrit, erythrocyte distribution, and erythrocyte transit time.24–26 These flow-dependent alterations provide another source for regional DL recruitment. Increasing blood flow minimizes regional variations in these dynamic erythrocyte characteristics, resulting in increased DL even while systemic hematocrit remains constant.

**Erythrocyte Shape**

Erythrocytes dynamically deform into parachute and other irregular shapes during capillary transit; deformation minimizes flow resistance but may also reduce DLCO,27 presumably by shielding part of the erythrocyte membrane from the capillary surface.28 Hence, erythrocyte deformation exerts a tradeoff by improving flow distribution while increasing diffusive resistance to gas exchange as Q increases. The net result under varying physiological conditions remains to be defined.

**Erythrocyte Distribution**

At a given hematocrit, free hemoglobin solution offers less resistance to carbon monoxide uptake than whole blood, ie, packaging hemoglobin into discrete cells significantly reduces DLCO and DMCO and promotes uneven erythrocyte distribution within and among capillaries. Erythrocyte distribution is difficult to quantify in vivo, although gross redistribution of perfusion, as in acute unilateral pulmonary artery occlusion, reduces DL in dogs.30 Simulation shows that DMCO should be highest when capillary erythrocytes are evenly spaced,31 and lowest when the same erythrocytes are tightly clustered, because adjacent erythrocyte surfaces become less effective in carbon monoxide uptake; random erythrocyte distribution yields intermediate values. Similarly, DMCO should be enhanced when erythrocytes are distributed uniformly among several capillary segments. At rest, erythrocyte distribution is typically nonuniform, since capillaries particularly at the lung apices are partially collapsed, allowing plasma flow but not erythrocyte flow. At exercise, increased flow, pressure, and dynamic erythrocyte distortion improves the uniformity of flow as well as distribution of erythrocytes with respect to alveolar surface, ie, improving the diffusion-perfusion matching. Simulations suggest that improving erythrocyte distribution alone without changing other parameters can account for 30 to 50% of the increase in DMCO observed from rest to peak exercise.31

**Physiologic Significance of Diffusion-perfusion Matching**

The oxygenation of blood during transit through the pulmonary capillaries is described by the Bohr integral,32 which graphically illustrates the relationship between ratio of DL/O2 to Q (DL/Q) and end-capillary oxygen saturation (Sc'O2) [Fig 3, right]. DL/O2 can be approximated by (1.65 × DLCO) [Fig 1]. For a given alveolar P02, mixed venous oxygen saturation, and blood oxygen tension at which binding sites on hemoglobin are 50% saturated, there exists a critical region of DL/Q, below which Sc'O2 falls sharply. For example, one could estimate how low DL/Q must become before Sc'O2 declines to 90%. As Q increases during exercise, DL must also

![DLCO/Q vs Cardiac Output](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21984/ on 05/31/2017)

**Figure 3.** Left: The DL/Q ratio declines from rest to exercise. Right: Relationship between end-capillary oxygen saturation and DL/Q estimated by the Bohr integral using data of Hsia et al.60
increase proportionately if a given DL/Q and ScO₂ is to be maintained. Normally, DL does not increase as rapidly as \( Q \) during exercise; hence, DL/Q ratio progressive declines from rest to exercise (Fig 3, left). Since the DL/Q ratio rather than the absolute DL determines SaO₂, arterial hypoxemia can develop even as DL continues to increase. In the average untrained subject, exercise is limited when a relatively low maximal \( Q \) is reached; at peak exercise, DL/Q does not decline sufficiently to affect SaO₂. Exercise training does not increase DL at a given \( Q \), but simply extends the linear DL-vs-Q relationship to a higher maximal \( Q \), allowing DL/Q to decline further and cause an exaggerated fall in SaO₂ at peak exercise (Fig 3, right). Thus, exercise-induced hypoxemia in top endurance athletes is a natural and expected consequence of selective cardiovascular conditioning.

The usual explanation for incomplete oxygenation of blood leaving the lung due to impaired diffusion is a low mean transit time of blood through the lung (\( \Delta t \)), i.e., a shortened time that capillary blood is in contact with gas exchange surface. Mean \( \Delta t \) is difficult to measure directly, but can be estimated indirectly from \( Q \) and \( Vc \), as shown in equation 4:

\[
\Delta t = \frac{Vc}{Q}
\]

Normally, \( \Delta t \) is about 0.75 to 1.0 s at rest and about 0.5 s at peak exercise. Increasing \( Q \) not only decreases \( \Delta t \), but causes regional distribution of \( \Delta t \) to become more uniform. A low \( \Delta t \) results from a high \( Q \), as in athletes at peak exercise, or low \( Vc \) as in obliterative processes such as emphysema, pulmonary fibrosis, or vascular disease. A reduced \( \Delta t \) is only one component within the classic concept of diffusion-perfusion (DL/Q) matching; the latter more comprehensively explains the mechanisms of alveolar blood oxygenation, analogous to ventilation-perfusion matching. Changes in physical properties of erythrocytes discussed above can significantly influence regional distribution of DL/Q ratios and alter SaO₂ without changing mean \( \Delta t \). For example, leukocytes are selectively and nonuniformly sequestered in pulmonary capillaries, obstruct capillaries and redirect regional erythrocyte traffic, shown by intravital videomicroscopy. Capillary segments distal to trapped leukocytes are devoid of erythrocytes and cannot participate in oxygen uptake. Altered leukocyte rheology seen in experimental inflammation and sepsis as well as human adult respiratory distress syndrome and hemodialysis can profoundly influence erythrocyte distribution, potentially causing uneven regional DL/Q ratios and reducing mean DL/Q and SaO₂ without changing mean \( \Delta t \). Additionally, in early interstitial pneumonitis where septal membrane may be thickened without obliteration of capillary bed, the DL/Q ratio is reduced even though mean \( \Delta t \) is normal.

**CLINICAL UTILITY OF DL**

**Assessing Response to Exercise**

There is ongoing controversy whether interstitial pulmonary edema develops in normal subjects after prolonged intense exercise. Serial measurements of breath-holding DLCO progressively fall over 4 to 6 h after a bout of intense exercise to 85% of resting pre-exercise control values; DmCO, DLNO, and \( Vc \) also decline independently of the type of exercise. The reduction in DLCO correlates with blood volume shifts from central circulation to the periphery, but not with indices of alveolar-capillary injury. A second bout of intensive exercise may or may not further reduce DLCO, but SaO₂ does not decline more than during the first exercise bout; results support a progressive fall in \( Vc \) due to fluid shifts but not interstitial fluid accumulation in normal subjects after intense exercise at sea level. These studies show that DL could be used to follow acute pulmonary microvascular changes.

**Assessing Lung Growth**

Champion swimmers have significantly higher lung volumes and DLCO at a given exercise intensity than average subjects of comparable age, attributed to a higher \( Vc \); differences may be partly due to genetic selection. Increasing ventilation and metabolic oxygen demand in animals via chronic cold exposure or induced hyperthyroidism have not led to enhanced lung growth or morphometric DL estimated from structural parameters at postmortem. DL correlates with enhanced lung growth in two models: high-altitude exposure and pneumonectomy. Natives born and raised at high altitude have higher lung volumes, DLCO, DMCO, and \( Vc \) than natives raised at sea level; differences persist even after reacclimatization to sea level. Immature dogs raised to maturity at high altitude show higher alveolar surface area, lung volume, and resting DLCO than control animals simultaneously raised at sea level. In immature dogs undergoing 55% lung resection by right pneumonectomy, vigorous compensatory lung growth returns resting DLCO to normal within 8 weeks. After reaching maturity, DLCO up to peak exercise is completely normal (Fig 4, right), associated with normalization of septal cell volume and alveolar-capillary surface areas. In adult
dogs, there is no compensatory lung growth after 45% lung resection by left pneumonectomy; rather, recruitment of DLCO reserves in the remaining lung is the major source of functional compensation (Fig 4, left). Recruitment increases DLCO per lung unit by nearly 50%, mitigating the expected decline in SaO2, and maintaining a near-normal exercise capacity. In adult dogs after 55% lung resection by right pneumonectomy, physiologic reserves alone could not maintain adequate gas exchange during exercise, and limited compensatory septal tissue growth is also stimulated, associated with a progressive increase in DL with respect to Q. Physiologic DL measured at peak exercise correlate highly with DL estimated from structural parameters in the remaining lung postmortem. In addition, perturbation in exercise SaO2 due to postpneumonectomy diffusion limitation could be accurately tracked from changes in DL. Thus, the DL/Q relationship can be used to noninvasively assess septal tissue growth.

Assessing Alveolar Disease

When some alveolar units are destroyed by disease, ventilation and blood flow are diverted, causing septal and capillary distension in the remaining lung units. The functional result is greater utilization of available diffusion reserves in the remaining units and more uniform matching between erythrocyte and tissue diffusion surfaces, i.e., recruitment of DL. Lung disease reduces DL at a given Q, leading to a low DL/Q, but recruitment of remaining alveolar-capillary units increases DL along the lower relationship (Fig 4, left) and provides functional compensation by maintaining the DL/Q ratio above that required for adequate oxygenation of blood. Because of large capillary reserves, resting DL may not accurately reflect the severity of anatomic disease, e.g., a 30% reduction of resting DL implies significantly > 30% loss of capillary bed.

The importance of DL recruitment as a compensatory mechanism for gas exchange is illustrated in Figure 5. The reduction in resting DLCO in patients after unilateral pneumonectomy who have a relatively normal remaining lung (FEV1 > 70% predicted for one lung) and patients with moderate-to-advanced interstitial pulmonary fibrosis is similar. In pneumonectomized patients, reserves of DL in the remaining lung units could be recruited. From rest to exercise, DLCO increases along a normal slope with respect to Q; hence, the decline in DL/Q ratio is mitigated and arterial hypoxemia may not occur during exercise or is only modest. SaO2 generally remains > 90%. In contrast, in pulmonary fibrosis there is little diffusive reserve; DLCO does not increase during exercise. As a result, the DL/Q ratio drops precipitously and early profound arterial hypoxemia constitutes an important source of exercise limitation. A similar impairment in DLCO recruitment has also been reported in pulmonary sarcoidosis.

DL may be an indicator of subclinical alveolar involvement in systemic disease. Resting DLCO, DMCO, and Vc are all reduced in asymptomatic patients with end-stage renal failure; increasing systemic hematocrit enhances resting DLCO and Vc, while changes in DMCO are directly related to the duration of hemodialysis. In patients with

Pulmonary Blood Flow

**Figure 4.** Mechanisms compensating for impaired diffusive transport: recruitment of DL and lung regrowth. **Left:** Alveolar disease reduces DL at a given pulmonary blood flow. Blood flow and ventilation, redirected to the remaining functioning alveoli, cause those units to distend, thereby increasing gas exchange surface area and DL along the lower relationship (arrows along dashed curve); apparent DL is higher than expected from anatomic alveolar destruction, but the upper limit of DL is lower. **Right:** Growth of new alveolar-capillary units restores DL at any given pulmonary blood flow back to normal (arrows).
Raynaud phenomenon without overt pulmonary dysfunction, cold-induced digital vasospasm is associated with an acute decline of resting DLCO and Vc consistent with pulmonary vasospasm, while DMCO remains unchanged. In asymptomatic young patients with long-standing insulin-dependent diabetes mellitus, DLCO at a given cardiac index is significantly reduced due to a lower DMCO compared to age-matched nondiabetic subjects, likely reflecting lung volume restriction and thickening of epithelial basement membrane. DL impairment is directly related to glycemic control, being most impaired in poorly controlled diabetics with chronic hyperglycemia, and least impaired in patients who are chronically maintained near normoglycemia through intensive insulin therapy. These observations are consistent with the strong correlation between glycemic control and retardation of extrapulmonary complications of insulin-dependent diabetes mellitus.

Assessing Cardiac Disease

In congestive heart failure (CHF), symptoms and exercise capacity correlate poorly with left ventricular hemodynamic function. Secondary dysfunction of locomotive and respiratory muscles as well as pulmonary gas exchange have emerged as important predictors of disability. In stable CHF, resting DMCO is disproportionately reduced with respect to V̇A, consistent with structural alteration of the alveolar membrane, such as interstitial edema, thickening, or fibrosis, while V̇e changes variably. The reduction of resting DMCO correlates directly with New York Heart Association functional class and maximal oxygen uptake and inversely with pulmonary vascular resistance, while an increased V̇e is seen in severe CHF consistent with microvascular congestion. Abnormal DLCO does not improve after cardiac transplantation, suggesting irreversible alveolar damage and/or immunosuppressive effects. However, there is often a reversible component of reduced DLCO in CHF. Acute saline solution infusion transiently increases V̇e and decreases DMCO in CHF patients. In some patients, pulmonary artery pressure may increase in response to dobutamine infusion associated with a decline in DLCO, likely reflecting impaired microvascular recruitment or distension. Inhibition of angiotension-converting enzyme increases DMCO and DLCO and decreases V̇e, presumably through reduction of pulmonary capillary pressure; improved DL is accompanied by lower dead space ventilation and improved exercise tolerance. In spite of the low DL in CHF, SaO₂ does not usually fall during exercise. Since the primary impairment is impaired Q̇ and recruitment of DL remains normal, (Fig 5), DL/Q̇ usually does not decline sufficiently at peak exercise to cause arterial hypoxemia, again illustrating the need to consider Q̇ in interpreting DL.

Summary

In summary, this review emphasizes several major concepts:

1. Given the consistent relationships of DLCO, DLNO, and DLO₂ to Q̇ from rest to exercise, DLCO and DLNO can be used to interpret the effectiveness of diffusive oxygen transport.

2. The ability to appropriately recruit DL and match regional diffusion-perfusion (DL/Q̇) ratios is critical for maintaining a normal SaO₂ at rest and exercise. In destructive lung disease, recruitment of DL in the remaining alveolar units determines whether severe arterial hypoxemia develops. Measured DLCO should be interpreted not only with respect to lung volume and hemoglobin concentration, but also with respect to Q̇. Established methods that simultaneously measure DL, Q̇, and lung volume using multiple tracer gases such as slow exhalation and rebreathing techniques offer distinct advantage over the routine breathholding method for DLCO alone. The former tech-
Techniques have not been widely utilized because of their expense and technical complexity. The availability of affordable, rapid-response multigas infrared analyzers has made these systems more accessible for clinical use. Simultaneous measurement of DLNO and DLCO reduces the time and effort required for estimating membrane and erythrocyte resistances, and could facilitate wider application of these indices. Exercise measurements can detect occult diffusion abnormalities, and are helpful whenever interpretation of resting data is unclear.

(3) Gas uptake across the alveolar membrane and erythrocytes are interdependent steps, and both are affected by hemoglobin concentration. Factors that alter erythrocyte distribution also alter DL recruitment and DL/Q matching. Empirical correction factors routinely applied to normalize DLCO to a standard hemoglobin concentration do not account for the interdependence and should be interpreted with this limitation in mind.

(4) Although DL has been clinically used for decades, it was only recently established that DL measured physiologically at peak exercise correlates with that estimated from structural constituents of the alveolar-capillary barrier. The structure-function correspondence highlights the sensitivity of DL and its components as noninvasive indicators of the integrity of pulmonary microvascular bed, and consolidates the scientific foundation supporting their application in the evaluation of exercise response, lung growth, overt and subclinical cardiopulmonary disease, as well as response to therapeutic intervention.

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